IN THE UNITED STATES DISTRICT COURT FOR THE MIDDLE DISTRICT OF TENNESSEE NASHVILLE DIVISION

RUTH SMITH, Individually and as Widow for the Use and Benefit of Herself and the Next of Kin of Richard Smith, Deceased,	)	
Plaintiff,	)	Civil No. 3:05–0444 Judge Aleta A. Trauger
v.	)	
PFIZER INC., *et al.,*	)	
Defendants.		

REVISED TESTIMONY OF ROBERT GIBBONS[1]

My name is Robert D. Gibbons, and I am the Director of the Center for Health Statistics, and Professor of Biostatistics, Mathematics, Statistics, Computer Science and Psychiatry at the University of Illinois at Chicago. I am a Fellow of the American Statistical Association and a two-time recipient of the American Statistical Association's Youden Award for statistical contributions to the field of Chemistry (2001 and 2006), and the 2009 Outstanding Statistical Application Award for the development of new and innovative statistical approaches to drug safety, and for clarifying the relationship between antidepressant pharmacotherapy and suicide. I have received the Harvard Award for lifetime contributions to the field of Psychiatric Epidemiology and Biostatistics. I am a member of the Institute of Medicine of the National Academy of Sciences (NAS),

[1] Revised testimony is noted in redline.

and served for six years on the Institute of Medicine Board on Health Science Policy.

I am the author of over 200 peer reviewed scientific papers, and five books. Two of these books are considered foundational in the area of environmental statistics (Statistical Methods for Groundwater Monitoring (1st edition 1994, 2nd edition 2009); and Statistical Methods for Detection and Quantification of Environmental Contamination (2001) with David Coleman, both published by John Wiley and Sons), and the 2001 book received the distinction of being in the top 5 books for statisticians, from the American Statistical Association. My most recent book with Don Hedeker "Longitudinal Data Analysis," also published by John Wiley and Sons in 2006 and now being updated to a 2nd edition, presents a comprehensive overview of methods for the analysis of longitudinal data, with particular emphasis on analytic problems in mental health research. My first book, "Statistical and Methodological Advances in Psychiatric Research," was published in 1982.

I have served as a member on the Institute of Medicine Committee on the Prevention of Suicide, and developed the statistical Appendix of that report that provides a state of the art presentation of statistical methods for the analysis of suicide completion and attempts. I also served on the Institute of Medicine Committee on U.S. Drug Safety, which recommended major changes in the way in which the FDA evaluates safety and post- marketing surveillance of pharmaceuticals. These recommendations have been adopted by Congress and are now being implemented at FDA. I personally wrote the recommendation that led to the new FDA Sentinel Network that is using large scale medical records and claims data to evaluate post-marketing drug surveillance. I was recently elected to the Sentinel Network Safety Science Board. I also served on the FDA Scientific Advisory

Committee on Suicide and Antidepressants in Children. My colleagues and I have recently published five peer reviewed papers on the relationship between antidepressants and suicide. These papers included U.S. county-level analyses of the relationship between antidepressants and suicide in (1) the general population (*Archives of General Psychiatry*, 2005) and (2) in children (*American Journal of Psychiatry*, 2006) in the United States, (3) a study of 226,000 depressed U.S. veterans (*American Journal of Psychiatry*, 2007), (4) a study of changes in antidepressant prescriptions and youth suicide rates in the U.S. and Europe before and after public health advisories in the U.S., U.K., and Europe, and black box warning in the U.S (*American Journal of Psychiatry*, 2007), and (5) a statistical paper that develops a new approach to the analysis of spontaneous report data, illustrated with an example of antidepressants and suicide from the FDA Adverse Event Reporting System (AERS) data (*Statistics in Medicine*). Our recent paper, published in the *Archives of General Psychiatry* explicates the relationship between antiepileptic drugs and suicide attempts in a cohort of almost 50,000 patients with bipolar disorder. We looked at patients with bipolar illness, because among patients treated with antiepileptic drugs, patients with bipolar illness are at the highest risk of suicide. Finally, I am the primary author of the chapter on post-marketing drug surveillance chapter of the 2010 Annual Review of Public Health. My CV describes in detail my educational and professional experience and it is marked as **EXHIBIT 7434.**

In this litigation, I was asked to evaluate the FDA meta-analysis of anti-epileptic clinical trial data. I was also asked to present the results of my own pharmacoepidemiologic study based

on a large scale medical claims database.

I have prepared a slide summarizing my opinions in this matter **[SHOW DEMONSTRATIVE: DR. GIBBONS' OPINIONS]**. First, the FDA meta-analysis does not demonstrate that Gabapentin is even associated with -- let alone causes -- suicidal thinking and behavior. Second, my own study of AEDs in almost 50,000 bipolar patients, who are at the highest risk of suicide, shows that these drugs do not increase the risk of suicide attempts. Third, my study of gabapentin in over 130,000 patients with epilepsy, psychiatric and other illnesses demonstrates that gabapentin does not increase the risk of suicide attempts. Fourth, there is no basis for a suicide warning specific to gabapentin because there is no signal of increased risk. I hold these opinions to a reasonable degree of medical certainty.

I would like to first discuss the FDA AED meta-analysis. As a general background, meta-analysis is a way of combining the evidence from many randomized clinical trials, and as such, it is a tool for data review. It is a way to summarize the data from many individual clinical trials or studies. Although meta-analyses are very useful methods for research synthesis, they are not useful for deriving causal inferences in and of themselves. It is my opinion that it is not proper to take the results of a combined meta-analysis of studies of 11 different antiepileptic drugs to make a statement that any one of them causes suicide.

We are going to be talking about a number of different statistical terms today. So, I would like to provide you with some basic definitions. First, we will be discussing a calculation called the odds ratio. This is the ratio of the probability of experiencing an adverse effect on a drug relative to placebo or the absence of treatment. So an odds ratio of 2 indicates that the probability of experiencing the adverse event on drug is double the probability of experiencing it on placebo. An odds ratio of 1 would indicate that the probability for placebo and active drug are identical, and an odds ratio .5 would mean that the drug has half the probability of an adverse event relative to placebo.

Another term is confidence interval. In a single experiment, we obtain an estimate of the odds ratio or some other summary statistics. If we were to repeat the experiment we would get a different estimate of the odds ratio. The confidence interval provides a range of possible values for the true value of the odds ratio in the real world, based on the results of a single experiment. In practice, we use a confidence level of 95% for the confidence interval.

Let's talk now about FDA's meta-analysis. FDA sought to answer the question whether there was a potential for increased risk of suicidality (suicide behavior or ideation) from the use of anti-epileptic drugs. In March of 2005, FDA sent letters to sponsors of 11 AEDs requesting the submission of suicidality data from placebo-controlled clinical trials. Based on FDA's analysis of these data, on January 31, 2008, they issued an alert to health care

providers regarding increased risk of suicidal thoughts and behavior with AEDs. While details of the analysis were extremely limited in the alert, on May 23, 2008, FDA released a report on the details of their statistical review and evaluation of these data. The FDA has indicated that the meta-analyses, such as this one, do not indicate a causal link between these drugs and suicidality. **[SHOW DEMONSTRATIVE: 12/2008 ALERT]**.

I have prepared a slide summarizing my opinions regarding the FDA AED meta-analysis. **[SHOW DEMONSTRATIVE: CRITICISMS OF FDA 2008 STUDY]**. –First, 2 of the AEDs studied, topiramate and lamotrigine, are solely responsible for the conclusion that AEDs as a group are associated with increased risk of suicidal thinking and behavior. If these two drugs were not a part of the study, there would be no Alert. Second, FDA excluded the vast majority of gabapentin studies which had zero events in both treated and control arms, retaining only the three studies for which there were suicidal thoughts, one in each study. This method eliminates almost all of the information, which creates an impression of risk that is not supported by the analysis. Third, because suicidal thinking and behavior are rare, and FDA included studies with different drugs given for very different indications, it is wrong to conclude that the findings based on 11 AEDs apply to any one drug. Fourth, FDA's conclusions of increased risk do not apply to all patients. In fact, FDA's analysis shows that there is no increased risk in North Americans, or psychiatric patients, or non-hospitalized patients, or women.

I would like to now discuss each of these opinions in some detail. Plaintiffs' experts have made much of the fact that FDA Alert says the "findings are consistent" among the drugs tested in this analysis. Let me first show you what FDA found. **[SHOW DEMONSTRATIVE: CASES OF SUICIDAL BEHAVIOR OR THINKING]**. This plot shows the number of suicidality events (the number above each bar) and the total number of patients studies for each drug (the number in parentheses above each bar) for each of the 11 AEDs. As you can see, by far and away, the vast majority of events occurred with lamotrigine (27 events) and topiramate (40 events). These two drugs contributed 38% of patients to the analysis but had 61% of the events. Gabapentin, or Neurontin, on the other hand, had only 2 events out of 2903 patients treated. This very clearly shows that the results are not "generally consistent."

[SHOW DEMONSTRATIVE: FDA META-ANALYSIS ODDS RATIOS FOR ALL 11 AEDS]. This is what is known as a "forest plot," and it shows the odds ratios (the solid symbols) and the confidence intervals (shown by the bars on either side of the symbols) for each of the AEDs. The data are plotted in this fashion in order to get a sense of the results for each drug. As a general rule of thumb, with regards to odds ratios, when the confidence interval includes 1.0, the finding for that particular drug is not statistically significant. For example, gabapentin (shown by the red square) had an odds ratio of 1.57, but the confidence interval was 0.12 to 47.66 showing that there was not a statistically significant increased

risk for suicidality with gabapentin, that is, the probability of having a suicidal thought on gabapentin or placebo is the same because the confidence interval includes the value 1.0. On the other hand, topiramate (the third blue circle from the bottom) had an odds ratio of 2.53 with a confidence interval of 1.21 to 5.86, which is a statistically significant increase risk because it does not include the value 1.0. Lamotrigine (the blue circle under gabapentin) had an odds ratio of 2.08 with a confidence interval of 1.03 to 4.40, which is also a statistically significant increase risk. If you take a moment to review this graph, you will see that topiramate and lamotrigine are the only 2 individual drugs with an increased risk for suicidality. Again, this shows how the results are not generally consistent.

Using these data, I determined that the findings are not "consistent" among the AEDs tested. I performed my own analysis to see if the effect FDA found is from topiramate and lamotrigine compared to the other nine drugs. **[SHOW DEMONSTRATIVE: RATE OF SUICIDAL BEHAVIOR AND THINKING FOR TOPIRAMATE & LAMOTRIGINE – PART 1]**. I compared the difference between the nine other AEDs against placebo and lamotrigine and topiramate against placebo. This plot shows the rate of suicidality events for patients treated with lamotrigine or topiramate (red bar) compared to placebo (grey bar). This shows that treatment with either lamotrigine or topiramate results in a doubling of the probability of a suicidal thought or behavior. **[SHOW DEMONSTRATIVE: RATE OF SUICIDAL BEHAVIOR AND THINKING FOR TOPIRAMATE & LAMOTRIGINE – PART 2]**.

Compare this now to the odds ratio for patients treated with the other nine AEDs (blue bar) compared to placebo (dark grey bar). Here, you see that there is no difference between the other nine drugs and sugar pill. It is important to note that there is a very low rate of suicide thoughts and behavior for all drugs – even those with highest risk, lamotrigine and topiramate, there is less than a 1% incidence. If, nine of these drugs show no effect, the result cannot be "consistent" across all drugs. Based on the fact that lamotrigine and topiramate, drove the results and the other nine drugs show no increased risk, FDA's findings are not "generally consistent" among all the drugs. It is my opinion, to a reasonable degree of scientific certainty, that if lamotrigine and topiramate had never been part of this analysis, FDA would not have found that AEDs increase the risk for suicidality. If the study contained only these 9 drugs, and not lamotrigine and topiramate, there would never have been an Alert or an AC meeting or a new warning.

My second opinion regarding the FDA meta-analysis speaks to FDA's exclusion of trials where no suicidality events were recorded. FDA threw out all studies with zero events – which represents the vast majority of the gabapentin data. Gabapentin had only 2 events of suicidal thinking – not attempts or completed suicides and there was 1 event in the much smaller number of placebo patients. Each was in a different study, leaving only three studies of gabapentin that FDA was able to use in their analysis. This is sign of a really safe drug. By throwing out all of the zero event studies it makes it appear that a much smaller

group of patients was studied, and that a difference between 2 suicidal thoughts on drug and 1 on placebo is meaningful. Which it clearly is not.

As a way of checking the impact of excluding zero-event trials, FDA did a meta-analysis of risk differences, which did not require the exclusion of zero-event studies. A risk difference is basically the difference in the rate of suicidality on drug versus the rate of suicidality on placebo. A risk difference of 0 means that there is no risk, and if the confidence interval includes the value 0, the result is not statistically significant. **[SHOW DEMONSTRATIVE: FDA META-ANALYSIS RISK DIFFERENCES FOR ALL 11 AEDS]**. Here again is forest plot of the risk differences (shown by the symbols) and the corresponding confidence intervals (shown by the lines). Here, FDA found that for gabapentin, the estimated risk difference was only 0.28 suicidal thoughts per 1000 patients (i.e., one quarter of a patient more experiencing a suicidal thought treated with gabapentin relative to placebo). The confidence interval was from -1.37 to 1.92, indicating that there is no statistical evidence of suicidality risk for patients treated with gabapentin. By contrast, the estimated risk difference for lamotrigine was 5.40 per 1000 patients treated and for topiramate the risk difference was 3.05 per 1000 patients treated, both of which were statistically significant. This is summarized in the following plots. **[SHOW DEMONSTRATIVE: RISK DIFFERENCE COMPARISON – GABAPENTIN VERSUS LAMOTRIGINE AND TOPIRAMATE – PART 1].** This plot shows the risk difference for lamotrigine (pink bar), topiramate (gold bar) and gabapentin (blue bar).

[SHOW DEMONSTRATIVE: RISK DIFFERENCE COMPARISON – GABAPENTIN VERSUS LAMOTRIGINE AND TOPIRAMATE – PART 2]. The risk difference for lamotrigine is 19 times higher than for gabapentin, and the risk difference for topiramate is 11 times larger than for gabapentin. Again, these findings raise serious questions regarding the "consistency" of results among members of this class of drugs. Furthermore, these data make it clear that for gabapentin, there is no increased risk of suicidality.

My third opinion regarding the FDA meta-analysis is that it is wrong to conclude that these results can be applied to any one drug. Because suicidal thinking and behavior are rare events, and because FDA included 11 drugs that are very different with very different indications and types of underlying studies, it is wrong to conclude that the findings from this study are "generally consistent." The bottom line is that because of the differences in the results for these AEDs, compared to the overall finding by FDA, one cannot attribute the overall data to any one drug. This can be shown on the next slide. **[SHOW DEMONSTRATIVE: FDA CONCLUSIONS CANNOT BE APPLIED TO GABAPENTIN]**. This shows the number of events of suicidal thinking and behavior for the FDA pooled analysis (red bar). There were a total of 104 events. If you apply this rate to the gabapentin data, we would expect to have seen 22 events (middle bar). But, gabapentin actually only had 2 events. This shows that the FDA meta-analysis findings should not be applied to gabapentin.
To illustrate my point, applying the combined results of the meta-analysis to gabapentin would be like taking a baseball team's batting average and using it to draw conclusions

about the batting average of an individual player. A baseball team can have some very good hitters and some very bad hitters, and the team batting average is a combination of all of the player's batting averages and tells us very little about the batting averages of the individual players. For example, if you put me on a team with a lot of very good professional baseball players, the team batting average is likely to be high, but that does not change the fact that I would not connect with a single pitch. So, combining gabapentin data in the same way with other antiepileptic drugs with individually elevated risk, does not reliably tell us anything about gabapentin individually.

My fourth opinion criticizing the FDA meta-analysis is that the conclusions of increased risk do not apply to all patients. This gives rise to additional serious concerns regarding the consistency of these data. **[SHOW DEMONSTRATIVE: DO FDA's CONLCUSIONS APPLY TO THESE GROUPS]**. First, for studies conducted in North America, there was no signal for a significant association between antiepileptic drugs and suicidality (OR=1.38, CI=0.90-2.13). Second, for patients treated for psychiatric indications, there was no signal for a significant association between antiepileptic drugs and suicidality (OR=1.51, CI=0.95-2.45). Third, for inpatients, there was no signal for a significant association between antiepileptic drugs and suicidality (OR=1.42, CI=0.40-5.62). Fourth, for females, there was no signal for a significant association between antiepileptic drugs and suicidality (OR=1.39, CI=0.85-2.35). These subgroup analyses that were performed by FDA, are inconsistent with their conclusion that the data show a consistent picture of

increased risk of suicidality for all antiepileptic drugs.

There is a claim in this case that GABAergic drugs in particular carry an increased risk of suicidal behavior. As you will recall from earlier testimony, stated simply, a GABAergic drug is one that acts to affect the levels of the brain neurotransmitter, GABA. I do not have an opinion one way or another as to whether gabapentin is GABAergic. Although FDA's analysis did look at different mechanism classes of drugs to evaluate the risk of suicide, FDA unfortunately put topiramate, which had the most events, in all of the pharmacologic groups. This makes any analysis of whether there is difference in risk profiles among the different classes of drugs problematic, as is shown in the next 3 slides. **[SHOW DEMONSTRATIVE: EFFECT OF REMOVING TOPIRAMATE FROM GABAERGIC GROUP – PART 1]**. This is my own analysis of these data. This slide shows a forest plot of the odds ratio for the GABAergic drugs, and it shows a statistically significant increased risk with an odds ratio of 1.80. **[SHOW DEMONSTRATIVE: EFFECT OF REMOVING TOPIRAMATE FROM GABAERGIC GROUP – PART 2]**. If you look only at the data for topiramate, there is a statistically significant increased risk with an odds ratio of 2.53. **[SHOW DEMONSTRATIVE: EFFECT OF REMOVING TOPIRAMATE FROM GABAERGIC GROUP – PART 3]**. If you remove the topiramate data from the GABAergic group, you no longer see an increased risk; the odds ratio becomes 1.01 with a confidence interval of 0.51 to 2.02. The conclusion from this analysis is that topiramate is driving the results for the GABAergic group. In other

words, if topiramate is excluded from the group, one would conclude that GABAergic drugs have no increased risk for suicidality.

So what happened with this analysis? First, FDA's primary analysis was based solely on studies with events, and since the majority of the events were for lamotrigine and topiramate, studies of those two drugs dominated the primary meta-analysis. Second, FDA's analysis did not adequately test for study to study and drug to drug variability in the effect of treatment on suicidality. When treatment effects vary across studies and/or drugs, it is invalid to attribute the overall effect to any one study or any one drug. So for example in this case, the overall odds ratio of 1.8, does not apply equally to all antiepileptic drugs. Third, FDA relied upon the consistency of the effects between drug classes as support for the consistency of the effects for the individual drugs. In fact, when topiramate is removed from the secondary drug-class analyses there is no signal whatsoever for GABAergic drugs where sufficient data are available for a meaningful analysis. To conclude that "the results were generally consistent among all the different drug products" is not supported by the available data.

On July 10, 2008, FDA convened a meeting of two of their scientific advisory boards to determine the type and extent of the public health warning that FDA will put out regarding AEDs and suicidality. The committee voted against placing a black box warning on AEDs for suicidality. I completely agree with the decision of the committee. A black box warning is the highest level warning for a pharmaceutical issued by the FDA. I do not believe there is any statistical justification for any suicide warning on the basis of the

Neurontin data. It is my unequivocal opinion that meta-analysis cannot be used for drawing causal inferences, especially with respect to any individual drug within the pooled dataset.

To date there have been few studies of the relationship between antiepileptic drugs and suicidal thoughts and behavior. I have conducted such a study. **[SHOW DEMONSTRATIVE: DR. GIBBONS' PUBLISHED BIPOLAR STUDY]**. I call this study the "bipolar study."

In an attempt to better understand if a possible relationship between AEDs and suicide exists, I conducted a study of a cohort of 47,918 patients with a diagnosis of bipolar disorder who had an observation period of one year before diagnosis and a follow-up period of one year after diagnosis. I selected patients with bipolar disorder because among all patients treated with antiepileptic drugs they are at the highest risk for suicide. I chose to analyze suicide attempt because it is closer to the event of most interest, which is suicide, and occurs in great enough numbers to permit analysis in a medical claims database. Further, since completed suicides are not likely to generate medical claims, as opposed to suicide attempts, I chose the later for purposes of my analysis. Data for this study came from the PHARMetrics database, the largest national database of health care claims data that is commercially available. These national data are not statistically different from the 2000 U.S. Census distributions of age, gender, and region. The universe of data are comprised of medical, specialty, facility, and pharmacy paid claims from more than 85

managed care plans nationally, representing more than 47 million covered lives. Pfizer had no control over the study design or analyses or how the study was written. Pfizer never saw a draft of the article before it was submitted to the journal for publication. Pfizer has not edited a single word of the paper. I did not do anything differently in this study than I have done in my other studies where I was working with a database supplied by a vendor or through a grant from a government agency.

The bipolar study has been published in the peer-reviewed journal *Archives of General Psychiatry*. This is significant for several reasons. First, this study was not conducted for litigation. Second, this journal is one of the most prestigious journals in psychiatry. Third, publication means that the study and findings were subjected to peer-review by highly qualified scientists who made comments on the initial draft that were addressed by more analysis; and then the journal concluded the study was reliable and of scientific importance for publication. Fourth, this journal has the highest "impact factor" of all psychiatric journals – meaning the studies published in it are most often cited by other authors of scientific publications.

For this study, data were collected from fiscal years 2000 through 2006. All patients with a diagnosis of bipolar disorder and had continuous enrollment in the system one year before and after diagnosis were included in the sample. Analyses were adjusted for age, sex, prior suicide attempts and concomitant treatment (other AEDs, antidepressants, antipsychotics, and lithium).

Here is what I found in the bipolar study. **[SHOW DEMONSTRATIVE: DR. GIBBONS' PHARMETRICS STUDY OF BIPOLAR PATIENTS]**. This slide shows that rate of suicide attempts (per 1000 patient years) for patients pre-AED treatment and with AED treatment. So, when you look at bipolar patients who received any one of the 11 AEDs in the FDA Alert after being diagnosed with bipolar disease and compare them to patients who did not receive an AED after diagnosis, those who received AED treatment did not have an increased risk of suicide attempt. Comparing suicide attempt rates before and after treatment, there was a significant reduced risk from 72/1000 patient years to 13/ 1000 patient years. **[SHOW DEMONSTRATIVE: DR. GIBBONS' BIPOLAR STUDY – BETWEEN SUBJECT COMPARISONS]**. This slide shows, on the left-hand pair of bars, that following treatment there was no overall significant difference in SA rates for patients treated with an AED (13/1000py) versus patients not treated with an AED or lithium (13/1000py); this means no statistically significant difference between BP patients who got an AED and those that didn't. On the other hand, in patients receiving no additional treatment with another drug such as an antidepressant, other AEDs or antipsychotic, AEDs had significantly decreased risk relative to no pharmacologic treatment (15/1000 PY versus 3/1000 PY), as shown on the right-hand pair of bars. These findings are consistent with FDA's meta-analysis which also found no evidence of increased risk of suicidality for patients treated with gabapentin.

To check my findings, I performed a second analysis, using monthly data for each patient and comparing the risk of suicide attempts between those months that were covered by an AED

prescription versus those months that were not. In this way, a patient who took an AED in the first month following the index episode of bipolar illness only contributed a single person month to the exposure period and all months thereafter would be considered unexposed (i.e., no treatment with an AED). While the primary analyses are conservative in that they classify all post treatment suicide attempts as drug related, it can be argued that this also inflates the length of the treatment period by attributing all post-treatment months to the treatment time period. For example, one can imagine a situation where all patients take a drug for only one month, but all suicide attempts occur in that month. By attributing the entire post-treatment period to drug, one may underestimate the effect of AED treatment on suicide attempt rate. The statistical approach that I used, allowed me to determine if the treatment effect was underestimated in this way. This analysis also allowed me to determine if there was regression towards the mean (that is, the natural decrease in suicide attempt rate over time), and if present, to adjust for it. If drug treatment continues to produce a significant decrease in suicide attempt rate, this analysis then rules out the previously described alternative explanation. **[SHOW DEMONSTRATIVE: DR. GIBBONS' BIPOLAR STUDY – PERSON-TIME ANALYSIS]**. I found that the significant decrease in suicide attempt rate on drug was further validated by the monthly analysis. This slide shows that there was a significant decrease in suicide attempt rate with AED treatment (blue line) relative to no AED treatment (red line). My analysis revealed that the rate of suicide attempts with AED treatment was statistically significantly lower than the rate without AED treatment. The odds ratio that I calculated for this analysis was OR=0.59, CI=0.47-0.75, $p<0.0001$, which means that AEDs were associated with a significantly lower rate of suicide attempts in this high-risk patient population.

[SHOW DEMONSTRATIVE: PERSON-TIME ANALYSIS OF HIGHEST RISK GROUP - BIPOLAR PATIENTS WITH SUICIDE ATTEMPT IN PRIOR YEAR].

When I restricted the analysis to only those 662 patients that made a suicide attempt in the year prior to the index diagnosis, I found that there was an even larger decrease in suicide attempt rate associated with treatment (OR=0.35, CI=0.17-0.74, $p<0.005$). This is an even higher risk population, because patients with a prior suicide attempt are 12 times more likely to make another attempt in the next year.

What does this study tell us generally about treatment of patients with AEDs? It tells us first, that patients who were treated with AEDs had a statistically significant reduction in suicide attempt rate after taking AEDs than before. In other words, for patients who ultimately received AED treatment, their rate of suicide attempt was significantly *lower* after being treated with an AED than before. The study also tells us that the suicide attempt rate in patients who ultimately got AEDs was higher than in the no-treatment group. It is my opinion, to a reasonable degree of scientific certainty, these data show that not only do AEDs *not* increase the risk of suicide behavior, but if anything, there may be a reduced risk for suicide attempt in these patients. That is, there may be protective effect of AEDs for suicide attempt.

The results of my study on bipolar patients addresses the theory in the case expressed by plaintiffs' experts Drs. Kruszewski, Trimble, Glenmullen and Blume that individuals who have suicide risk are "vulnerable" and "susceptible" to the effects of gabapentin and other

AEDs. This entire study is on that group of individuals that – if plaintiffs' experts' theory were correct – these patients would be the *most* vulnerable to AEDs like gabapentin. Published studies show that patients with bipolar disorder have the highest risk of suicide behavior out of all psychiatric disorders. If there was ever a group to test a "vulnerable subpopulation" theory in, this is it. Furthermore, the secondary analysis in prior attempters is an even higher risk sample. My study shows the opposite. Gabapentin does NOT increase the risk of suicide behavior in people at the highest risk for suicide. And in fact, "vulnerable" people at the highest risk of suicide behavior had a statistically significantly *lower* risk after taking AEDs, including gabapentin.

Next, I did a study looking at the PhARMetrics database to assess whether patients who were taking gabapentin had increased risk of suicide behavior; I call this study the "gabapentin study." I conducted a separate study not just looking at bipolar patients, but looking at 131,178 patients who took gabapentin – for any indication – to see if they had increased risk of suicide attempt after initiation of gabapentin treatment. These patients had conditions such as psychiatric disorders (major depressive disorder, schizophrenia, bipolar disease, and other psychiatric disorders), epilepsy, and pain disorders. I analyzed all 131,178 gabapentin patients as a group, but then also analyzed them based on their underlying conditions to see if subgroups might have increased suicide risk after taking gabapentin. Not only did I adjust for other drugs that were taken, such as antidepressants, antipsychotics, and other antiepileptics, I looked at a subgroup of patients who ONLY took

gabapentin, to rule out any confounding effects of patients taking other psychiatric medications. Patients who take multiple psychiatric medications (e.g., antidepressants, antipsychotics and multiple AEDs), are generally more severely impaired and/or treatment resistant and will be at higher risk for suicide. By including these concomitant treatments in my analysis, I can adjust for differences in severity between patients receiving single versus multiple treatments.

I found that the risk of suicide attempt in gabapentin patients prior to treatment is low 30/100,000 PY, but it is cut almost in half after taking gabapentin (16/100,000 PY).

[SHOW DEMONSTRATIVE: DR. GIBBONS' GABAPENTIN STUDY – ANALYSIS BY DIAGNOSIS]. This slide shows the odds ratios for gabapentin and suicide attempt for several of the diagnoses I investigated. In this analysis, when all patients are grouped together (shown by the bottom blue circle labeled "All"), there was no increased risk of gabapentin for suicide attempt. Gabapentin significantly decreases suicide attempt rates in these more severely ill patients with psychiatric illnesses, which is shown in the top three blue circles. These data suggest that there may be a possible protective effect in psychiatric patients taking gabapentin. For epilepsy and pain patients, I found no increased risk, but also no statistically significant decrease in risk.

I performed a similar monthly analysis to that described earlier for the bipolar cohort for the gabapentin cohort. **[SHOW DEMONSTRATIVE: DR. GIBBONS' GABAPENTIN STUDY – PERSON-TIME ANALYSIS]**. This slide shows the rate of the suicide attempts (per 100,000

person months) for gabapentin treated (blue line) patients and patients receiving no treatment (red line). Results of the analysis revealed a significant overall effect of gabapentin use on suicide attempts (OR=0.73, CI=0.55-0.97, p<0.03), indicating reduced risk of suicide attempts while patients are receiving treatment with gabapentin.

Now I'll address three very recent studies, which I'll refer to as Patorno, Olesen and VanCott. Plaintiff's experts talked about Patorno and Olesen, but didn't mention VanCott. One of Plaintiff's experts, Dr. Greenland, suggests that the study by Patorno and colleagues supports FDA's conclusions regarding the relationship between AEDs and suicidality. Another one of Plaintiff's experts, Dr. Blume, contends that this article provides scientific and reliable evidence that is consistent with the opinion that gabapentin can cause depression and suicidal behavior. I disagree with both positions.

Patorno was an exploratory study that compared rates of suicide, attempted suicide, and violent deaths in users of ten different AEDs, including gabapentin, to the rates of the same events in users of another AED, topiramate. The first important thing to understand about this study is that it did not include a comparison group of patients who were given placebo, or a comparison group of patients who were not given any treatment. As such, this study cannot tell us whether patients taking gabapentin are at increased risk of suicidal behavior relative to patients not receiving AED treatment. As the authors note, their results could only evaluate the rate of suicidality in gabapentin users "compared with the use of topiramate or carbamazepine." Stated differently, the Patorno study does not tell us

anything about whether patients receiving AEDs are at increased risk of suicide compared to patients who receive no drug.

To understand why this is the case, consider a hypothetical study in which the rate of an event of interest is 30% in placebo-treated patients. Now imagine that we compare the placebo to three different drugs. The rate of the event in patients treated with the first drug, which I'll call drug A, is 15%, the event in the second drug, which I'll call drug B, is 20%, and the third drug, drug C, is 5%. If we look at the event rates in just the drug-treated patients, which is what is done in studies like Patorno, we see significant differences in rates. In fact, if we calculate the relative risk of drug B versus drug C, which is simply 20% divided by 5%, we get a relative risk of 4.0, indicating a quadrupling of risk. This is an increased risk in drug B compared to drug C that is far in excess of the increase found in the Patorno study for gabapentin versus topiramate. But if we calculate the relative risk of drug B versus placebo, 20% divided by 30%, we get a relative risk of 0.67. This is an indication that the rate of the event is decreased in patients treated with drug B, and that drug B is potentially protective for the event. In other words, in this hypothetical, even though the drugs have different risk estimates when compared with one another, all three of the drugs have a lower incidence of the event compared to placebo, and all three are potentially protective for the event. Without looking at the placebo group, we don't know whether drugs A, B and C increase or decrease the risk of the event. The same is true of the Patorno study.

Another point that becomes clear from this illustration is the difference in the conclusions we can reach based on the drug we choose as a reference. If I'm studying drug A and I pick drug B as a reference, drug A will appear protective. The relative risk is 15% divided by 20%, or 0.75. If I choose drug C, the relative risk is 15% divided by 5%, or 3.0, and drug A appears to triple the rate of the event. Once again, this tells me nothing about the real risk of the event in patients treated with drug A versus placebo, because we know that the placebo rate is actually higher than the rate for drug A.

Turning back to the Patorno study, we can't even be sure that the observed differences in rates of suicide events between patients using gabapentin and patients using topiramate represent any real difference in drug effects, because the different rates could represent differences in the types of patients who are prescribed the two drugs by their physicians. Despite their best attempts to adjust for potential confounding, there is no guarantee that the authors have eliminated all of the measured and unmeasured characteristics that could produce differences in suicide behavior rates between the different drugs. These residual differences may have nothing to do with the effects of the drug on suicidality.

[Demonstrative: Raw and Adjusted Figures for Gabapentin]

It is important to note that, in the un-adjusted analysis, relative to topiramate, the rate of suicide attempts, completed suicides, and violent deaths is lower for gabapentin. As you can see in this chart, which simply shows the figures for gabapentin compared to topiramate from the Patorno study, the raw numbers showed less suicide attempts, completed suicides and violent deaths in gabapentin patients. It is only following statistical adjustment for potential confounding variables that the estimated rate of suicidal behavior appears to be elevated for gabapentin. Again, this study provides no evidence that gabapentin increases suicidal behavior relative to untreated patients or relative to periods of time when these same patients did not receive gabapentin.

One other issue should be addressed. The authors eliminated all patients who made a suicide attempt in the six months before initiation of treatment. In many ways, these are the most important patients to study because they are at the highest risk of future suicidal behavior. We have no way of knowing what the results of this study would have been if those patients were included. In both of my studies, I performed analyses that were restricted to prior attempters and found decreases in suicide attempt rates with treatment in these patients who are at the highest risk for suicide.

Another important thing to understand about the Patorno study is that its results were inconsistent with the conclusion of the Plaintiff's experts, and the FDA, that all AEDs have the same effect on the incidence of suicidality. Far from finding that the rates were the

same, the Patorno study found statistically significant differences in the rates of suicide and attempted suicide in patients who were treated with different AEDs.

One final point on the Patorno study. Dr. Blume suggests that this study somehow supports the conclusion that gabapentin increases the risk of depression. There is simply nothing in the Patorno study that could support such a conclusion. The study did not perform any statistical analysis on depression rates, and certainly did not find any increased risk for gabapentin.

The Plaintiff's experts also rely on a recent study by Olesen and colleagues. This study used two methods to evaluate completed suicide in AED users. First, they used a fairly difficult-to-explain method called a case-crossover design, which compares exposure rates to a drug during time-periods close to the event (in this case suicide) relative to periods of times further away from the event. Second, they conducted a cohort study similar to Patorno, which compared the incidence of suicide in ten AEDs relative to a reference AED, carbamazepine. Results of both of these analyses showed no statistically significant effect of gabapentin on completed suicide.

[Demonstrative: Figure 2 from Olesen]

As you can see from this figure from the study, gabapentin had the lowest hazard ratio of any of the AEDs relative to carbamazepine. Importantly, gabapentin also had a substantially lower completed suicide rate than topiramate. This is inconsistent with the conclusion, which Plaintiff's experts seek to draw from the Patorno study, that gabapentin is associated with a higher suicide risk than topiramate. For these reasons, I strongly disagree with the conclusion that Olesen supports an increased risk of suicide for gabapentin.

Another study, by VanCott and colleagues, which Plaintiff's experts simply ignore, compared suicide attempt rates in patients receiving gabapentin with rates in patients receiving other AEDs. This was also a drug versus drug study, and suffers from the same limitations as the Patorno study. However, in this study the authors found that newer AEDs (levetiracetam and lamotrigine) had a statistically significant 10-fold higher rate of suicide attempts than gabapentin. In addition, this study found a higher rate of suicide attempts for carbamazepine relative to gabapentin, although this difference was not statistically significant. The finding of this study also contradict the conclusions of the Patorno study.

[Demonstrative—Result of Various Observational Studies]

I have prepared a chart to provide a summary of what the various studies actually demonstrate about the relationship between AEDs and suicidality. What we can see from this chart summarizing these analyses is that the results are all over the map. Some find

increased and some find decreased rates of suicidality in patients treated with various AEDs compared to patients treated with gabapentin. The only striking consistency is that none of them support the conclusion that the drugs have the same effects on suicidality. None of these new observational studies can support a conclusion one way or the other about whether gabapentin increases suicide risk, because of the lack of an unexposed comparison group. As you can see in the right-hand column, the only studies that used either a placebo control or untreated comparison groups were the FDA study, the first Olesen analysis, and my two studies. None of these studies found a statistically significant increased risk of suicidality with gabapentin treatment.

The Plaintiff's experts know very well that the Patorno and Olesen papers by themselves do not support a conclusion that gabapentin increases the risk of suicide. In an attempt to compensate for this problem, Dr. Greenland has taken one of the calculations from the Patorno study, the hazard ratio for attempted and completed suicide for topiramate versus gabapentin, which is 1.42, and multiplied it by the odds ratio calculated in FDA's analysis for suicidal thoughts and behavior for topiramate versus placebo, which is 2.53. The resulting estimate is 3.6, which he argues represents the risk for suicidality in gabapentin versus placebo. This calculation defies all principles of sound statistical practice. I have never read a publication suggesting that this is a valid method, and never in my 30 years of experience as a professor of biostatistics, have I heard of anyone employing it.

There are several obvious problems that render Dr. Greenland's calculation meaningless. For one thing, the events in the two studies are different; the Patorno paper included only suicide attempts and completed suicides, while the FDA analysis included suicidal thoughts. In fact, most of the events in FDA's analysis were suicidal thoughts. Another problem is that the population in the FDA analysis was different from the population in the Patorno study. Dr. Greenland's calculation is a bit like multiplying a measurement in pounds by a measurement in kilograms. The result is meaningless.

In addition, Dr. Greenland's calculation is the result of cherry picking an isolated number from a study to support his results. To show how unreliable his estimate is, I performed the same computation with other rate calculations from these studies. For example, taking the other comparison drug used in the Patorno article, carbamazepine, the calculated relative risk was 1.45 and the odds ratio from the FDA analysis was 0.65. Multiplying these two numbers together results in a risk estimate of 0.94. Under Dr. Greenland's reasoning, this represents a small decrease in suicidality risk in gabapentin patients compared to placebo. As another example, taking the odds ratio from FDA's analysis for lamotrigine of 2.08 and the odds ratio from the VanCott article for gabapentin compared to lamotrigine of 0.098 we find that the resulting estimate for the comparison of gabapentin to placebo is now 2.08 times 0.098=0.20, or one fifth the likelihood of gabapentin producing something to do with suicide than placebo. Again, my opinion is that these are totally unreliable calculations and

I certainly wouldn't suggest that these numbers prove that gabapentin decreases suicide risk, but this shows how completely meaningless Dr. Greenland's computations are in this case.

In conclusion, it is my opinion to a reasonable degree of scientific certainty that, as to FDA's analysis of AEDs, there is simply no scientific evidence that AEDs increase the risk of suicidal behavior. In fact, when you look at AEDs alone – with no other medications or lithium – it is clear based on these results that AEDs are associated with a significant reduction in the risk of suicide attempts (when compared to no treatment), and when compared to the pre-treatment suicide attempt rate in these individuals. These bipolar patients who are eventually treated with AEDs are sicker – they have a higher pre-treatment suicide attempt rate – are at higher risk of attempting suicide than others. Yet, when they go on to get treatment, that risk is significantly reduced.

The findings from my study are dramatic for gabapentin – the gabapentin patients were at 6 times less risk of suicide attempt after taking gabapentin. This finding shows that if anything, gabapentin protects against risk of suicide attempts.

Gabapentin does not increase the risk of suicide attempt – especially in patients who the plaintiffs' experts say are "vulnerable" or "the susceptible minority". In fact, in those

patients with psychiatric illness – major depressive disorder and bipolar disease – gabapentin treatment was associated with significantly *lowered* risk of suicide attempt.

Also, my findings for gabapentin are in line with the FDA data for gabapentin alone, which show that gabapentin does NOT increase risk of suicidality.

Based on all of the evidence that I have reviewed, and the data that I have personally analyzed, it is my opinion that there is no increased risk of suicidal thinking and behavior for gabapentin overall, and if anything, there may be protective effects for psychiatric patients who are at increased suicidal risk. Because no signal has been identified for increased risk of suicidality for gabapentin, there was never any reason for Pfizer to warn physicians of this non-existent risk.